```
      ---  -----  ----------
? s emapII or emap (w) II

            16  EMAPII
           258  EMAP
        776501  II
            85  EMAP(W)II
S1          98  EMAPII OR EMAP (W) II
? s s1 and (inhibit? or antisens? or ribozym? or antibod?)

            98  S1
       1885355  INHIBIT?
         30246  ANTISENS?
          5244  RIBOZYM?
       1058251  ANTIBOD?
S2          32  S1 AND (INHIBIT? OR ANTISENS? OR RIBOZYM? OR ANTIBOD?)
? rd

...completed examining records
S3          20  RD (unique items)
? t s3/3,ab/all


 3/3,AB/1      (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11624451   21433397   PMID: 11549594
  Control of stromal keratitis by inhibition of neovascularization.
  Zheng M; Schwarz MA; Lee S; Kumaraguru U; Rouse BT
  Department of Microbiology, University of Tennessee, Knoxville, Tennessee. Children's Hospital of Los Angeles, University of Southern California, Los Angeles, California.
  American journal of pathology (United States) Sep 2001, 159 (3) p1021-9, ISSN 0002-9440 Journal Code: 3RS
  Languages: ENGLISH
  Document type: Journal Article
  Record type: In Process
  Stromal keratitis resulting from ocular infection with herpes simplex virus is a common cause of blindness. This report investigates the role of neovascularization in the pathogenesis of stromal keratitis by measuring the outcome of treatment with the potent anti-angiogenesis cytokine endothelial monocyte-activating polypeptide II (EMAP II). We show that systemic and topical administration of EMAP II from the outset of infection resulted in markedly diminished levels of herpes simplex virus-induced angiogenesis and significantly reduced the severity of stromal keratitis lesions. EMAP II treatment had no demonstrable pro-inflammatory or toxic effects and failed to express antiviral activity. The mechanism of action of EMAP II was shown to proceed by causing apoptosis in vascular endothelial cells. Our data document for the first time the essential role of angiogenesis in the pathogenesis of stromal keratitis and also indicate that the therapy of herpetic stromal keratitis could benefit by procedures that diminish angiogenesis.


 3/3,AB/2      (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11568692   21406605   PMID: 11515784
```

Differential activati[redacted] of microglial cells in local [redacted] IRBP1[redacted]-1191-induced r[redacted]uveitis.
Fauser S; Nguyen TD; Bekure K; Schluesener HJ; Meyermann R
Institute of Brain Research, University of Tuebingen, Germany.
Acta neuropathologica (Germany) Jun 2001, 101 (6) p565-71, ISSN 0001-6322 Journal Code: 1CE
Languages: ENGLISH
Document type: Journal Article
Record type: In Process
Using a Lewis rat model of interphotoreceptor retinoid binding protein (IRBP)-induced experimental autoimmune uveitis (EAU) we examined cellular reactions in the optic pathway (retina, choroid, optic nerve, optic tract, colliculus superior, and visual cortex). Two to six animals were studied at days 6, 7, 9, 11, 12, 13, 14, 18 and 22 after immunization by immunohistochemistry with monoclonal **antibodies** against ED , ED2, OX6, OX22, **EMAP II**, AIF-1 and W3/13. In the retina, choroid and distal optic nerve increased immunoreactivity to ED1, OX6, OX22, **EMAP II** , AIF-1 and W3/13 was initially observed at day 9, peaked at days 13-14 and diminished rapidly from day 18 onwards. No changes were seen in the density of ED2-positive resident macrophages. In the optic tract, ED1 and OX6 expression was induced in microglial cells beginning with day 11 and persisted until day 22. AIF-1, **EMAP II** and ED2 expression was not visibly up-regulated and no lymphocytic infiltrates (OX22-, W3/13-positive cells) were observed. In the central projection fields, no cellular reaction could be found. Thus, cellular response in IRBP-induced rat uveoretinitis is not restricted to the eye. Microglial activation is also seen in the distal optic nerve and optic tract. This remote microglial activation, however, differs in intensity, time course and expression of activation markers, thus indicating different activation cascades. The mild remote microglial activation is probably due to neuronal-microglial interactions resulting from neuronal damage in the retinal ganglion cell layer and nerve fiber layer with consecutive axonal degeneration and not from an inflammatory reaction as seen in the eye.

3/3,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11239904 21122997 PMID: 11232242
Expression of **EMAP II** in the developing and adult mouse.
Knies UE; Kroger S; Clauss M
Department of Molecular Cell Biology, Max-Planck-Institute fur Physiologische und Klinische Forschung, Parkstrasse 1, 61231 Bad Nauheim, Germany.
Apoptosis (United States) Apr 2000, 5 (2) p141-51, ISSN 1360-8185 Journal Code: DWY
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Endothelial monocyte-activating polypeptide II (**EMAP II**) is a chemoattractant for monocytes and granulocytes. **EMAP II** is translated as a precursor protein, proEMAP II, and is proteolytically cleaved to become the mature, biologically active cytokine. In this study we show that the **EMAP II** mRNA and the **EMAP II** precursor protein are constitutively expressed by all cell types analyzed in vitro, whereas the mature cytokine is only present in the supernatant of apoptotic cells. During mouse embryogenesis we found widespread expression of the **EMAP II** mRNA with transcripts being abundant in areas of tissue remodeling, where a large number of apoptotic cells could be detected by TUNEL staining. In the adult mouse, strong expression of the **EMAP II** mRNA is restricted to the brain, testis and thymus. Interestingly, prominent signals for **EMAP II** mRNA are found in local correlation with sites of apoptosis in thymus and testis but not in the brain. We propose that during development, the generation and release of the mature **EMAP II** may provide a mechanism for the

adult brain, the generation of mature **EMAP II** may contribute to the recruitment of monocytes and the immunosurveillance of this tissue.

3/3,AB,4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10933300 20455183 PMID: 11001545
Endothelial monocyte-activating polypeptide II, a tumor-derived cytokine that plays an important role in inflammation, apoptosis, and angiogenesis.
Berger AC; Tang G; Alexander HR; Libutti SK
Metabolism Section, Surgery Branch, Division of Clinical Sciences, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA.
Journal of immunotherapy (UNITED STATES) Sep-Oct 2000, 23 (5) p519-27, Journal Code: CUQ
Languages: ENGLISH
Document type: Journal Article; Review; Review, Tutorial
Record type: Completed
The interactions between a tumor and its surrounding environment are complex and characterized by a variety of factors. Tumors produce a number of proteins that enable them to recruit a vascular supply, invade into surrounding tissues, and metastasize to distant sites. The host, in turn, responds to these signals by producing its own repertoire of molecules that may either assist or prevent the actions of the tumor. A thorough understanding of this relationship is critical to the development of novel anti-cancer therapies. The tumor-derived cytokine endothelial monocyte-activating polypeptide II (**EMAP-II**) has profound effects on the tumor as well as on host response. These effects target the inflammatory cascade as well as the processes involved in angiogenesis. In this review the authors describe the current understanding of the role of **EMAP-II** in inflammation, apoptosis, and angiogenesis and use this molecule to illustrate the complex interactions that occur in the tumor microenvironment.

3/3,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10895445 20560565 PMID: 11106577
Immunohistochemical analysis of endothelial-monocyte-activating polypeptide-II expression in vivo.
Murray JJ; Barnett G; Tas M; Jakobsen A; Brown J; Powe D; Clelland C
CRC Department of Clinical Oncology, University of Nottingham Laboratory of Molecular Oncology, Nottingham, United Kingdom. cliff.murray@nott.ac.uk
American journal of pathology (UNITED STATES) Dec 2000, 157 (6) p2045-53, ISSN 0002-9440 Journal Code: 3RS
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Endothelial-monocyte activating polypeptide (**EMAP**)-**II** is a novel molecule with cytokine-like pro-inflammatory properties, inducing procoagulant activity on the surface of endothelial cells and monocyte/macrophages in vitro, as well as up-regulating E- and P-selectin expression. **EMAP-II** is chemotactic for monocytes/macrophages and neutrophils, and stimulates myeloperoxidase release from neutrophils. Injection of **EMAP-II** into the mouse footpad induces an acute inflammatory response, although some regression occurs in response to direct injection of **EMAP-II** into murine tumors. Very little is known about the expression of **EMAP-II** in normal tissues of mice or humans, or about its function in vivo. We developed polyclonal **antibodies** against **EMAP-II** using recombinant protein produced in Escherichia coli, and used these **antibodies** to carry out an immunohistochemical study of the occurrence and distribution of

EMAP-II in human tiss[redacted]. The **EMAP-II** protein is relatively [redacted]stricted, occurring primarily [redacted]endocrine organs, in cells of neuroendocrine origin, but also in tissues with high turnover. **EMAP-II** is strongly expressed in secretory epithelial cells of the thyroid, pancreas, adrenal and salivary glands, among others, as well as in neurons and subsets of monocytes/macrophages. It is also found in the epithelium of the small and large intestines. We conclude that **EMAP-II** expression is usually, but not always, associated with tissues that display high turnover and high levels of protein synthesis.

3/3,AB/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10828888 20368162 PMID: 10906456
Endothelial monocyte activating polypeptide II **inhibits** lung neovascularization and airway epithelial morphogenesis.
Schwarz MA; Zhang F; Gebb S; Starnes V; Warburton D
Department of Pediatrics, Children's Hospital Research Institute, Los Angeles, CA 90027, USA. mschwarz@chla.usc.edu
Mechanisms of development (IRELAND) Jul 2000, 95 (1-2) p123-32, ISSN 0925-4773 Journal Code: AXF
Contract/Grant No.: HL-03981, HL, NHLBI; HL-44060, HL, NHLBI; HL-60061, HL, NHLBI; -
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Neovascularization is crucial to lung development and is mediated through a variety of angiogenic and anti-angiogenic factors. Herein, we show that excess Endothelial Monocyte Activating Polypeptide (**EMAP**) **II**, an anti-angiogenic protein, not only **inhibits** fetal lung neovascularization, but also significantly alters airway epithelial morphogenesis. In a murine allograft model of lung neovascularization and morphogenesis, embryonic lungs transplanted under the skin of immunocompromised mice receiving intraperitoneal **EMAP II**, had a 56% reduction in vessel density ($P<0.0001$) compared to control. **EMAP II** treated lung transplants also exhibited a marked alteration in lung morphogenesis, including lack of type II alveolar cell formation, determined by markedly decreased expression of surfactant protein C, and increased apoptosis. In contrast, lung implants in animals receiving an **EMAP II** blocking **antibody** had an increase in vessel density of 50% ($P<0.0001$) and increased expression of surfactant protein C mRNA in distal epithelium. These studies demonstrate that **EMAP II** negatively modulates lung neovascularization as well as leading to the arrest of lung airway epithelial morphogenesis and apoptosis.

3/3,AB/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10778598 20334744 PMID: 10873516
Endothelial monocyte activating polypeptide II induces endothelial cell apoptosis and may **inhibit** tumor angiogenesis.
Berger AC; Alexander HR; Tang G; Wu PS; Hewitt SM; Turner E; Kruger E; Figg WD; Grove A; Kohn E; Stern D; Libutti SK
Surgery Branch, National Cancer Institute, Bethesda, Maryland 20892, USA.
Microvascular research (UNITED STATES) Jul 2000, 60 (1) p70-80, ISSN 0026-2862 Journal Code: MXW
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Endothelial monocyte activating polypeptide II (**EMAP-II**) is a tumor-derived cytokine with potent effects on endothelial cells in vitro and in vivo including upregulation of tissue factor and the sensitization of human melanoma to systemic TNF treatment via its effects on the tumor

vasculature. We investigated the effects of **EMAP-II** on tumor growth, angiogenesis, vasculogenesis, and apoptosis. **EMAP-II** **inhibited** endothelial cell proliferation, vasculogenesis, and neovessel formation. In vivo growth of human melanoma lines expressing high amounts of **EMAP-II** demonstrated slower growth, smaller tumors, and increased amounts of tumor necrosis than those expressing lower amounts of **EMAP-II**. **EMAP-II** induced endothelial-cell-specific apoptosis via a pathway that includes upregulation of the Fas-associated death domain and downregulation of Bcl-2. **EMAP-II** appears to have important effects on angiogenesis and may play a role in regulating tumor vascular growth.

3/3,AB/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10712925 20340646 PMID: 10880244
Tumour necrosis factor receptor I (p55) is upregulated on endothelial cells by exposure to the tumour-derived cytokine endothelial monocyte-activating polypeptide II (**EMAP-II**).
Berger AC; Alexander HR; Wu PC; Tang G; Gnant MF; Mixon A; Turner ES; Libutti SK
Surgery Branch, National Institutes of Health, Bethesda, MD 20892, USA.
Cytokine (UNITED STATES) Jul 2000, 12 (7) p992-1000, ISSN 1043-4666 Journal Code: A52
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Endothelial monocyte activating polypeptide-II (**EMAP-II**) is an inflammatory cytokine known to have a role in neutrophil and macrophage chemotaxis and in apoptosis. It is a tumour-derived cytokine that sensitizes tumour vasculature to the effects of systemic TNF. In order to gain insight into the mechanism by which **EMAP-II** sensitizes vessels to TNF, we focused on its effects on TNF receptor expression. In human umbilical vein endothelial cells (HUVEC), TNF-R1 mRNA is increased four-fold following incubation with recombinant **EMAP-II**. Conditioned media from cell lines known to produce high levels of **EMAP-II** upregulated TNF-R1 but not TNF-R2 by up to twenty-fold compared to media controls and low expressing cell lines; this effect was blocked by anti-**EMAP-II antibody**. Recombinant **EMAP-II** upregulated TNF-R1 expression by approximately six-fold. Analysis of HUVEC lysates by ELISA showed increased expression of TNF-R1 within 2 h; TNF-R2 expression was unaffected by recombinant **EMAP-II**. Finally, immunohistochemistry of human melanomas in vivo showed that TNF-R1 staining is increased on the vessels of tumours known to express high levels of **EMAP-II** compared to low **EMAP-II** expressing tumours. These results suggest that **EMAP-II** upregulates TNF-R1 expression by endothelial cells both in vitro and in vivo. This induction of TNF-R1 expression may be the mechanism by which **EMAP-II** sensitizes tumour endothelium to the effects of TNF leading to haemorrhagic necrosis. Copyright 2000 Academic Press.

3/3,AB/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10698572 20399708 PMID: 10945611
Antiangiogenic treatment enhances photodynamic therapy responsiveness in a mouse mammary carcinoma.
Ferrario A; von Tiehl KF; Rucker N; Schwarz MA; Gill PS; Gomer CJ
Clayton Center for Ocular Oncology, Childrens Hospital Los Angeles, California 90027, USA.
Cancer research (UNITED STATES) Aug 1 2000, 60 (15) p4066-9, ISSN 0008-5472 Journal Code: CNF
Contract/Grant No.: CA-31230, CA, NCI; HL-03981, HL, NHLBI; HL-60061, HL,

NHLBI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Photodynamic therapy (PDT) is a promising cancer treatment that induces localized tumor destruction via the photochemical generation of cytotoxic singlet oxygen. PDT-mediated oxidative stress elicits direct tumor cell damage as well as microvascular injury within exposed tumors. Reduction in vascular perfusion associated with PDT-mediated microvascular injury produces tumor tissue hypoxia. Using a transplantable BA mouse mammary carcinoma, we show that Photofrin-mediated PDT induced expression of the hypoxia-inducible factor-1alpha (HIF-1alpha) subunit of the heterodimeric HIF-1 transcription factor and also increased protein levels of the HIF-1 target gene, vascular endothelial growth factor (VEGF), within treated tumors. HIF-1alpha and VEGF expression were also observed following tumor clamping, which was used as a positive control for inducing tissue hypoxia. PDT treatment of BA tumor cells grown in culture resulted in a small increase in VEGF expression above basal levels, indicating that PDT-mediated hypoxia and oxidative stress could both be involved in the overexpression of VEGF. Tumor-bearing mice treated with combined antiangiogenic therapy (IM862 or **EMAP-II**) and PDT had improved tumoricidal responses compared with individual treatments. We also demonstrated that PDT-induced VEGF expression in tumors decreased when either IM862 or **EMAP-II** was included in the PDT treatment protocol. Our results indicate that combination procedures using antiangiogenic treatments can improve the therapeutic effectiveness of PDT.

3/3,AB/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10697010 20340719 PMID: 10878614
Temporo-spatial distribution of endothelial-monocyte activating polypeptide II, an anti-angiogenic protein, in the mouse embryo.
Zhang F; Schwarz MA
Childrens Hospital Research Institute Los Angeles California, Los Angeles, California 90027, USA.
Developmental dynamics (UNITED STATES) Jul 2000, 218 (3) p490-8, ISSN 1058-8388 Journal Code: A9U
Contract/Grant No.: HL03981, HL, NHLBI; HL60061, HL, NHLBI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
We describe the temporo-spatial distribution of Endothelial-Monocyte Activating Polypeptide (**EMAP**) **II** in order to better understand what role this anti-angiogenic proteins may play in fetal development. In situ hybridization, immunohistochemistry, and Western analysis were performed on fetal, neonatal, and adult tissue. **EMAP II** was first detected only within the central nervous system on 9 days postcoitum (dpc). Subsequently, at 11 through 18 dpc, **EMAP II** expression was detected in the respiratory, central nervous, cardiovascular, urogenital systems, sense organs, and digestive tract. **EMAP II** mRNA and protein was localized to the epithelium, with its highest expression in neurons, blood vessels, and at sites of epithelial-mesenchymal interaction. The temporo-spatial distribution of **EMAP II** suggests that it could play an important role in morphogenesis of the vertebrate embryo.

3/3,AB/11 (Item 11 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10651021 20309730 PMID: 10787402
The cytokine portion of p43 occupies a central position within the eukaryotic multisynthetase complex.

Department of Biochem[redacted]y, the University of Mississi[redacted] Medical Center, Jackson, Mississippi 39216-4505, USA. mnorcum@biochem.ums[redacted]ed.edu
Journal of biological chemistry (UNITED STATES) Jun 16 2000, 275 (24) p17921-4. ISSN 0021-9258 Journal Code: HIV
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Multicellular eukaryotes contain a macromolecular assembly of nine aminoacyl-tRNA synthetase activities and three auxiliary proteins. One of these, p43, is the precursor of endothelial monocyte-activating polypeptide II (**EMAP II**), an inflammatory cytokine involved in apoptotic processes. As a step toward understanding this paradoxical association, the **EMAP II** portion of p43 has been localized within the rabbit reticulocyte multisynthetase complex. Immunoblot analysis demonstrates strong reaction of anti-**EMAP II** antiserum with p43, as well as cross-reactivity with isoleucyl-tRNA synthetase. Electron microscopic images of immunocomplexes show two **antibody** binding sites. The primary site is near the midpoint of the multisynthetase complex at the intersection of the arms with the base. This site near the lower edge of the central cleft is assigned to the C-terminal cytokine portion of p43. The secondary site of **antibody** binding is in the base of the particle and maps the location of isoleucyl-tRNA synthetase. These data allow refinement of the three-domain model of polypeptide distribution within the multisynthetase complex. Moreover, the central location of p43/**EMAP II** suggests a role for this polypeptide in optimizing normal function and in rapid disruption of essential cellular machinery when apoptosis is signaled.

3/3,AB/12 (Item 12 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10632184 20306600 PMID: 10850427
Prostate adenocarcinoma cells release the novel proinflammatory polypeptide **EMAP-II** in response to stress.
Barnett G; Jakobsen AM; Tas M; Rice K; Carmichael J; Murray JC
Cancer Research Campaign Department of Clinical Oncology, City Hospital, Nottingham United Kingdom.
Cancer research (UNITED STATES) Jun 1 2000, 60 (11) p2850-7, ISSN 0008-5472 Journal Code: CNF
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The proinflammatory protein endothelial monocyte-activating polypeptide II (**EMAP-II**) was first detected in supernatants of murine tumor cells by virtue of its ability to stimulate endothelial-dependent coagulation in vitro. The purified protein has pleiotropic effects on endothelial cells, monocytes, and neutrophils; however, its function in vivo is unknown, and the mechanism whereby it is released from cells is poorly understood. We investigated the expression of **EMAP-II** in human prostate adenocarcinoma specimens by immunohistochemistry and in LNCaP and DU-145 human prostate adenocarcinoma cells by reverse transcription-PCR, flow cytometry, and Western blotting. We then examined the effects of chemical and physiological stress on release and processing of **EMAP-II** by LNCaP and DU-145 cells. These cells constitutively express a Mr 34,000 form of **EMAP-II** that is retained intracellularly. Exposure to agents that induce apoptosis or, in some cases, necrosis induces the release of the Mr 34,000 form and further processing to the Mr 27,000 and Mr 22,000 forms. Hypoxia, but not heat shock, is a potent inducer of release and processing of biologically active **EMAP-II** by LNCaP and DU-145 cells. We suggest that release of **EMAP-II** by prostate adenocarcinoma cells as a consequence of treatment with anticancer agents or as a result of constitutive hypoxia may potentiate the effects of those agents through the localized activation of

3/3,AB/13 (Item 13 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10586921 20171086 PMID: 10704888
The molecular basis of lung morphogenesis.
Warburton D; Schwarz M; Tefft D; Flores-Delgado G; Anderson KD; Cardoso WV
Department of Surgery, The Developmental Biology Program, University of Southern California Keck School of Medicine and School of Dentistry, Los Angeles, CA, USA.
Mechanisms of development (IRELAND) Mar 15 2000, 92 (1) p55-81, ISSN 0925-4773 Journal Code: AXF
Contract/Grant No.: P01HL60231, HL, NHLBI; R01HL44060, HL, NHLBI; R01HL44977, HL, NHLBI; +
Languages: ENGLISH
Document type: Journal Article; Review; Review, Academic
Record type: Completed
To form a diffusible interface large enough to conduct respiratory gas exchange with the circulation, the lung endoderm undergoes extensive branching morphogenesis and alveolization, coupled with angiogenesis and vasculogenesis. It is becoming clear that many of the key factors determining the process of branching morphogenesis, particularly of the respiratory organs, are highly conserved through evolution. Synthesis of information from null mutations in Drosophila and mouse indicates that members of the sonic hedgehog/patched/smoothened/Gli/FGF/FGFR/sprouty pathway are functionally conserved and extremely important in determining respiratory organogenesis through mesenchymal-epithelial inductive signaling, which induces epithelial proliferation, chemotaxis and organ-specific gene expression. Transcriptional factors including Nkx2.1, HNF family forkhead homologues, GATA family zinc finger factors, pou and hox, helix-loop-helix (HLH) factors, Id factors, glucocorticoid and retinoic acid receptors mediate and integrate the developmental genetic instruction of lung morphogenesis and cell lineage determination. Signaling by the IGF, EGF and TGF-beta/BMP pathways, extracellular matrix components and integrin signaling pathways also directs lung morphogenesis as well as proximo-distal lung epithelial cell lineage differentiation. Soluble factors secreted by lung mesenchyme comprise a 'compleat' inducer of lung morphogenesis. In general, peptide growth factors signaling through cognate receptors with tyrosine kinase intracellular signaling domains such as FGFR, EGFR, IGFR, PDGFR and c-met stimulate lung morphogenesis. On the other hand, cognate receptors with serine/threonine kinase intracellular signaling domains, such as the TGF-beta receptor family are **inhibitory**, although BMP4 and BMPR also play key inductive roles. Pulmonary neuroendocrine cells differentiate earliest in gestation from among multipotential lung epithelial cells. MASH1 null mutant mice do not develop PNE cells. Proximal and distal airway epithelial phenotypes differentiate under distinct transcriptional control mechanisms. It is becoming clear that angiogenesis and vasculogenesis of the pulmonary circulation and capillary network are closely linked with and may be necessary for lung epithelial morphogenesis. Like epithelial morphogenesis, pulmonary vascularization is subject to a fine balance between positive and negative factors. Angiogenic and vasculogenic factors include VEGF, which signals through cognate receptors flk and flt, while novel anti-angiogenic factors include **EMAP II**.

3/3,AB/14 (Item 14 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10343610 99417692 PMID: 10487768
Inhibition of apoptosis induced by ischemia-reperfusion prevents inflammation.

Vandenabeele P; Buurman [redacted]
Department of General Surgery, University of Maastricht, 6200 MD Maastricht, The Netherlands.
Journal of clinical investigation (UNITED STATES) Sep 1999, 104 (5) p541-9, ISSN 0021-9738 Journal Code: HS7
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

Ischemia followed by reperfusion leads to severe organ injury and dysfunction. Inflammation is considered to be the most important cause of tissue injury in organs subjected to ischemia. The mechanism that triggers inflammation and organ injury after ischemia remains to be elucidated, although different causes have been postulated. We investigated the role of apoptosis in the induction of inflammation and organ damage after renal ischemia. Using a murine model, we demonstrate a relationship between apoptosis and subsequent inflammation. At the time of reperfusion, administration of the antiapoptotic agents IGF-1 and ZVAD-fmk (a caspase inactivator) prevented the early onset of not only renal apoptosis, but also inflammation and tissue injury. Conversely, when the antiapoptotic agents were administered after onset of apoptosis, these protective effects were completely abrogated. The presence of apoptosis was directly correlated with posttranslational processing of the endothelial monocyte-activating polypeptide II (**EMAP-II**), which may explain apoptosis-induced influx and sequestration of leukocytes in the reperfused kidney. These results strongly suggest that apoptosis is a crucial event that can initiate reperfusion-induced inflammation and subsequent tissue injury. The newly described pathophysiological insights provide important opportunities to effectively prevent clinical manifestations of reperfusion injury in the kidney, and potentially in other organs.

7/3,AB/15 (Item 15 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10333530 99125902 PMID: 9928822
Effects of autoantigen and dexamethasone treatment on expression of endothelial-monocyte activating polypeptide II and allograft-inflammatory factor-1 by activated macrophages and microglial cells in lesions of experimental autoimmune encephalomyelitis, neuritis and uveitis.
Schluesener HJ; Seid K; Meyermann R
Institute of Brain Research, University of Tubingen, Germany.
Acta neuropathologica (GERMANY) Feb 1999, 97 (2) p119-26, ISSN 0001-6322 Journal Code: 1CE
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

Endothelial-monocyte activating polypeptide II (**EMAP II**) and allograft-inflammatory factor-1 (AIF-1) are two proteins produced by activated monocytes and microglial cells. We now report expression of these factors during experimental therapy of rat neuroautoimmune diseases. Comparative analysis of two therapeutic strategies, treatment with high doses of recombinant autoantigens or with dexamethasone, revealed unexpected differences. High doses of autoantigen were most effective in experimental autoimmune encephalomyelitis and neuritis (EAE and EAN), but less effective in experimental autoimmune uveitis (EAU). Low and high doses of dexamethasone treatment greatly reduced the severity of EAE, EAN and EAU at day 11, but a relapse was observed between days 21 and 26. Only rather limited expression of **EMAP II** and AIF-1 is seen in the normal central nervous system (CNS). This constitutive expression is not abolished by dexamethasone treatment. In inflammatory autoimmune lesions of the rat CNS, prominent AIF-1 and **EMAP II** staining was seen with macrophages and monocytes. In particular, parenchymal microglial cells were now activated to express AIF-1 and **EMAP II**. In accordance with prevention of neurological signs, histological observations revealed that

AIF-1 in the CNS or peripheral nervous system and the massive expression of these factors by parenchymal microglial cells is **inhibited** by high doses of autoantigen. Dexamethasone prevented or abolished local expression of **EMAP II** and AIF-1 at days 10-16. However, an acute and severe relapse occurred in encephalomyelitis between days 20-26. In these cases, a smoldering expression of **EMAP II** and AIF-1 persisting long after cessation of neurological signs was observed. Thus, expression of **EMAP II** and AIF-1 by infiltrating activated macrophages is a marker of disease activity and expression of these factors could be used to demonstrate 'silent' lesions in the CNS and prolonged microglial cell activation. Apparently, AIF-1 and **EMAP II** immunoreactivity are tools to stage activation of monocytes and microglial cells in inflammatory lesions.

3/3,AB/16 (Item 16 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10292013 97404153 PMID: 9262239
Localization of endothelial-monocyte-activating polypeptide II (**EMAP II**), a novel proinflammatory cytokine, to lesions of experimental autoimmune encephalomyelitis, neuritis and uveitis: expression by monocytes and activated microglial cells.
Schluesener HJ; Seid K; Zhao Y; Meyermann R
Institute of Brain Research, University of Tubingen, Germany.
Glia (UNITED STATES) Aug 1997, 20 (4) p365-72, ISSN 0894-1491
Journal Code: GLI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Endothelial-Monocyte-Activating Polypeptide II (**EMAP II**) is a proinflammatory cytokine and chemoattractant of macrophages. In order to investigate the role of **EMAP II** in autoimmune lesions of the rat nervous system, we have used a synthetic gene to express **EMAP II** in E. coli and have produced monoclonal **antibodies** against **EMAP II**. Monoclonal **antibodies** are suited to demonstrate **EMAP II** in ELISAs, Western blots, and paraffin-embedded tissue sections. **EMAP II** was localized to monocytes/macrophages with rather selective staining of a minor rat monocyte subpopulation of lymphoid tissues such as spleen, lymph nodes or follicles of the gut. In the normal brain, cells of the perivascular but not parenchymal microglia were stained. We then investigated expression of **EMAP II** during experimental autoimmune encephalomyelitis (EAE), neuritis (EAN), and uveitis (EAU). Within the local inflammatory lesions infiltrating macrophages are prominently stained. In the diseased brain, **EMAP II** -positive microglial cells are not only found in the direct vicinity of the inflammatory infiltrate, but widespread activation is seen in the parenchyma. This is the first demonstration that **EMAP II** is present in autoimmune lesions. Immunostaining of microglial cells is noteworthy, as these cells are strategically placed regulatory elements of CNS immunosurveillance. **EMAP II** might be a factor regulating monocyte chemoattraction, endothelial cell activation and a regulator of microglial cell reactivity in autoimmune inflammation of the central nervous system.

3/3,AB/17 (Item 17 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10277477 99421266 PMID: 10493523
Sensitization of tumor necrosis factor alpha-resistant human melanoma by tumor-specific in vivo transfer of the gene encoding endothelial monocyte-activating polypeptide II using recombinant vaccinia virus.
Gnant MF; Berger AC; Huang J; Puhlmann M; Wu PC; Merino MJ; Bartlett DL;

Alexander HR) Liburd [redacted]
Surgery Branch, Natio[redacted] Cancer Institute, NIH, Bethes[redacted] Maryland 20892, USA.
Cancer research (UNITED STATES) Sep 15 1999, 59 (18) p4668-74, ISSN 0008-5472 Journal Code: CNF
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Tumor necrosis factor alpha (TNF-alpha) is a proinflammatory cytokine with potent experimental antitumor activity. Its clinical use in cancer treatment is severely limited by its considerable toxicity after systemic administration, and it is currently confined to isolated limb and organ perfusion settings. In this report, we introduce a novel concept of TNF-alpha-based gene therapy using the TNF-sensitizing properties of endothelial cell monocyte-activating polypeptide II (**EMAP-II**). We hypothesized that transfer of the **EMAP-II** gene into established TNF-resistant human melanomas would render these tumors sensitive to subsequent systemic TNF-alpha treatment. To achieve tumor selective gene delivery, we constructed a recombinant vaccinia virus encoding the human **EMAP-II** gene (vvEMAP). In vitro transfection of human melanoma cells led to the production of **EMAP-II** by these cells. Supernatants of vvEMAP-transfected tumor cells mediated the induction of tissue factor in endothelial cells. We characterized the pattern of gene expression after systemic administration of a recombinant vaccinia virus encoding a reporter gene in a murine in vivo model of s.c. human melanoma. Gene expression in tumor tissue was increased 100-fold as compared with normal tissue, providing evidence for tumor-selective gene delivery. Finally, human melanomas in nude mice were sensitized in vivo by transferring the **EMAP-II** gene using vvEMAP. Subsequent systemic administration of TNF-alpha led to tumor regression and growth **inhibition** of these previously TNF-resistant tumors ($P < 0.05$). This approach using gene therapy to sensitize primarily unresponsive tumors toward TNF-alpha may enhance the usefulness of TNF-alpha in clinical treatment strategies by increasing the window for the therapeutic application of the cytokine, thus reducing the dose necessary for antitumor responses and subsequently reduce toxicity.

8/3,AB/18 (Item 18 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10218425 99359488 PMID: 10430623
Endothelial-monocyte activating polypeptide II, a novel antitumor cytokine that suppresses primary and metastatic tumor growth and induces apoptosis in growing endothelial cells.
Schwarz MA; Kandel J; Brett J; Li J; Hayward J; Schwarz RE; Chappey O; Wautier JL; Zhabot J; Lo Gerfo P; Stern D
Department of Pediatrics, Columbia University, College of Physicians and Surgeons, New York 10032, USA. mschwarz@chla.usc.edu
Journal of experimental medicine (UNITED STATES) Aug 2 1999, 190 (3) p341-54, ISSN 0022-1007 Journal Code: I2V
Contract/Grant No.: HL42833, HL, NHLBI; KO2 HL03981, HL, NHLBI; KO2 HL60061, HL, NHLBI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Neovascularization is essential for growth and spread of primary and metastatic tumors. We have identified a novel cytokine, endothelial-monocyte activating polypeptide (**EMAP**) **II**, that potently **inhibits** tumor growth, and appears to have antiangiogenic activity. Mice implanted with Matrigel showed an intense local angiogenic response, which **EMAP II** blocked by 76% ($P < 0.001$). Neovascularization of the mouse cornea was similarly prevented by **EMAP II** ($P < 0.003$). Intraperitoneally administered **EMAP II** suppressed the growth of primary Lewis lung carcinomas, with a

human breast carcinoma-derived MDA-MB 468 cells were suppressed by >80% in **EMAP II** -treated animals ($P < 0.005$). In a lung metastasis model, **EMAP II** blocked outgrowth of Lewis lung carcinoma macrometastases; total surface metastases were diminished by 65%, and of the 95 metastases present, approximately 80% were **inhibited** with maximum diameter <2 mm ($P < 0.002$ vs. controls). In growing capillary endothelial cultures, **EMAP II** induced apoptosis in a time- and dose-dependent manner, whereas other cell types were unaffected. These data suggest that **EMAP II** is a tumor-suppressive mediator with antiangiogenic properties allowing it to target growing endothelium and limit establishment of neovasculature.

3/3,AB/19 (Item 19 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09926060 98445370 PMID: 9770485
Regulation of endothelial monocyte-activating polypeptide II release by apoptosis.
Knies UE; Behrensdorf HA; Mitchell CA; Deutsch U; Risau W; Drexler HC; Clauss M
Department of Molecular Cell Biology, Max-Planck-Institut fur Physiologische und Klinische Forschung, Parkstrasse 1, 61231 Bad Nauheim, Germany.
Proceedings of the National Academy of Sciences of the United States of America (UNITED STATES) Oct 13 1998, 95 (21) p12322-7, ISSN 0027-8424 Journal Code: PV3
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Endothelial monocyte-activating polypeptide II (**EMAP II**) is a proinflammatory cytokine and a chemoattractant for monocytes. We show here that, in the mouse embryo, **EMAP II** mRNA was most abundant at sites of tissue remodeling where many apoptotic cells could be detected by terminal deoxynucleotidyltransferase-mediated dUTP end labeling. Removal of dead cells is known to require macrophages, and these were found to colocalize with areas of **EMAP II** mRNA expression and programmed cell death. In cultured cells, post-translational processing of pro-**EMAP II** protein to the mature released **EMAP II** form (23 kDa) occurred coincidentally with apoptosis. Cleavage of pro-**EMAP II** could be abrogated in cultured cells by using a peptide-based **inhibitor**, which competes with the ASTD cleavage site of pro-**EMAP II** . Our results suggest that the coordinate program of cell death includes activation of a caspase-like activity that initiates the processing of a cytokine responsible for macrophage attraction to the sites of apoptosis.

3/3,AB/20 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12436787 BIOSIS NO.: 200000190239
Cytoplasmic and nuclear localization of tyrosyl-tRNA synthetase in higher eukaryotic cells studied by immunoelectronic microscopy.
AUTHOR: Fibkinska T A; Ivanova Ju L; Cherny N E; Popenko V I; Matsuka G Kh; Kornelyuk A I
JOURNAL: Biopolimery i Kletka 15 (5):p409-414 1999
ISSN: 0233-7657
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: Ukrainian; Non-English
SUMMARY LANGUAGE: English; Ukrainian; Russian

immunoelectronic microscopy in bovine kidney cells and fibroblasts of RAT1 line which have been treated by monoclonal **antibodies** T3 raised against bovine tyrosyl-tRNA synthetase an by complexes of protein A-colloidal gold. The localization of tyrosyl-tRNA synthetase has been revealed both in cytoplasm and in the nucleus of mammalian cells. Tyrosyl-tRNA synthetase is located in cytoplasm mainly in the vicinity of polyribosomes what supports the compartmentalization conception of the components of protein synthesis apparatus. A significant portion of synthetase detected in the nucleus is located mainly in the region of diffuse chromatin, and partly in the nucleolus. In general, localization of tyrosyl-tRNA synthetase in mammalian cells is very similar to the localization of p43 protein of codosome, a precursor of the **EMAP II** cytokine, which is highly homologous to the non-catalytic C-terminal domain of tyrosyl-tRNA synthetase. Nuclear localization of tyrosyl-tRNA synthetase implies that this enzyme is involved in some non-canonical functions in the nucleus of eukaryotic cell. It is possible that this function may be related to the export of mature tRNA from nucleus to cytoplasm.